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Supplementary Information

Flavin-Catalyzed Electrochemical Production of Adipic Acid from Lignin-Derived-Methoxycyclohexanone with Air and Water

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1. General

The NMR spectra were measured using JEOL JNM-L400 and JNM ECX-500 spectrometers (JEOL, Akishima, Japan) operating at 400 and 500 MHz, respectively, for ¹H and 100 and 126 MHz, respectively, for ¹³C using tetramethylsilane (TMS) or a solvent residual peak as the internal standard. The electrospray ionization mass (ESI-MS) spectra were recorded on a Bruker microTOFII-SHIY3 mass spectrometer (Bruker, Billerica, MA) using the positive or negative mode ESI-TOF method for acetonitrile solutions and sodium formate as the reference. The GC measurements were performed on a Shimadzu GC-2014 gas chromatograph (Shimadzu, Kyoto, Japan) equipped with a flame ionization detector (FID) using a Supelco Equity-5 (30 m x 0.25 mm) column. The mass spectra of the generated gas were measured using a gas chromatograph mass gaspectrometer. Electron spin resonance (ESR) spectra were recorded on a JEOL JES-FA100 spectrometer. The g value was determined using a standard marker, Mn²⁺/MgO, for calibration of the magnetic fields. The electrochemical oxygenation was conducted using ElectraSyn 2.0 (IKA, Staufen, Germany) with a 5 mL three-electrode setup, consisting of an Ag/Ag⁺ reference electrode and two Pt foil electrodes (IKA). The reference solution was prepared by weighing silver nitrate (42.5 mg, 0.250 mmol) and tetrabutylammonium perchlorate (855 mg, 2.50 mmol), vacuum drying them overnight, and dissolving them in dry acetonitrile (25 mL). The silver wire used for the reference electrode was rinsed with nitric acid and water, polished with 0.05 µm alumina powder (BAS, Tokyo, Japan), and dried before and after use. The Pt foil electrodes, used as working or counter electrodes, were rinsed with 1 M HCl aqueous solution and water, then immersed in acetonitrile and cleaned using an ultrasonic cleaner for 15 minutes before being dried.

2. Materials

All starting materials were purchased from Sigma-Aldrich (St. Louis, USA), FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan), Nacalai tesque (Kyoto, Japan), and Tokyo Kasei (TCI, Tokyo, Japan) and were used as received. 5-Ethyl-1,3-dimethyl-8-

trifluoromethylalloxazinium triflate (1a•TfO)^{S1}, 5-ethyl-1,3-dimethylalloxazinium triflate (**1b**•**TfO**)^{S1}, 5-ethyl-1,3,7,8-tetramethylalloxazinium triflate (**1c**•**TfO**)^{S2}, 5-ethyl-10-(2hydroxylethyl)-3,7,8-trimethylisoalloxazinium triflate (2a•TfO)^{S2}, 1,10-ethylene-3- $(3a \cdot TfO)^{S3}$, methyl-7-trifluoromethylisoalloxazinium chloride 1,10-ethylene-3-(**3b•TfO**)^{S4}, 1,10-ethylene-3,7,8trimethylisoalloxazinium chloride trimethylisoalloxazinium chloride (3c•TfO)^{S5}, and riboflavin tetraacetate (4)^{S6} were synthesized according to the previously reported method. 2-Hydroxycyclohexanone (HCH) was synthesized according to the previously reported method.^{S7}

3. Experimental Procedures

Typical Procedure for Electrochemical Flavin-Catalyzed Reaction of MCH. The electrochemical oxygenation was conducted using ElectraSyn 2.0 (IKA, Staufen, Germany) with a 5 mL three-electrode setup, consisting of two Pt foil electrodes and an Ag/Ag⁺ reference electrode. A mixture of 2-metoxycyclohexanone (MCH, 65.6 mg, 0.51 mmol), LiOTf (78.0 mg, 0.50 mmol), 1a TfO (12.2 mg, 0.025 mmol), CH₃CN (4.0 mL), and H₂O (1.0 mL) was stirred under constant-potential electrolysis (-0.60 V vs Ag/Ag⁺) at 25 °C for 5.5 h with air bubbling at 1 atm using a peristatic pump (1.2 mL/min). After the solvent was removed by evaporation, 1 M NaHCO3 aqueous solution (5 mL) was added to the residue and washed with ethyl acetate (20 mL). The resulting aqueous phase was then treated with 1 M HCl aqueous solution (6 mL), and after confirming that the pH was 1 or below, the mixture was stirred at 60 °C for 40 hours and extracted with ethyl acetate (88 mL). The organic phase was dried over sodium sulfate, filtered, concentrated under reduced pressure using a rotary evaporator, and dried under vacuum to afford the desired product, AA (56.9 mg, 76%), as a milky white solid. This procedure is also applicable to 2-hydroxycyclohexanone (HCH), as summarized in Table 3.

Spectroscopic data of adipic acid (**AA**)^{S8}: Typical Procedure
afforded the desired product (56.9 mg, 76%) as a milky
white solid. ¹H NMR (500 MHz, (CD₃)₂CO, 25 °C,
$$\delta$$
): 10.55

(br s, 2H), 2.34-2.30 (m, 4H), 1.67-1.62 (m, 4H). ¹³C{¹H} NMR (126 MHz, (CD₃)₂CO, 25 °C, δ): 174.5, 33.6, 24.8.



2 mmol Scale synthesis of AA. The electrochemical oxygenation of **MCH** on a 2.0 mmol scale was also conducted using ElectraSyn 2.0 (IKA) with a 20 mL three-electrode setup, consisting of two Pt foil electrodes and an Ag/Ag⁺ reference electrode. A mixture of **MCH** (256 mg, 2.0 mmol), LiOTf (312 mg, 2.0 mmol), **1a**·**TfO** (48.8 mg, 0.10 mmol), CH₃CN (16 mL), and H₂O (4.0 mL) was stirred under constant-potential electrolysis (-0.60 V vs Ag/Ag⁺) at 25 °C with air bubbling at 1 atm using an air pump (12 mL/min). After 20 h of electrolysis, the crude product was esterified with trimethylsilyldiazomethane (TMSCHN₂) in the presence of methanol, and the resulting methyl ester of **AA** was analyzed by GC. The desired product was obtained in 63% yield. This yield is somewhat lower than that obtained on the 0.5 mmol scale (76% yield, 5.5 hours), which we attribute to the lower current density resulting from the use of the same electrode surface area in the absence of a larger electrochemical setup. Nevertheless, the reaction proceeded cleanly and without complication, suggesting that further scale-up would be feasible with appropriate equipment.

ESR Measurements of Fl_{rad} . The formation of the flavin radical intermediate was confirmed by the ESR measurement using a reaction mixture of $1a \cdot TfO$ obtained after 10 min of stirring under the following condition (Figure 1A). A mixture of $1a \cdot TfO$ (12.2 mg, 0.025 mmol), LiOTf (78.1 mg, 0.50 mmol), and dry CH₃CN (5.0 mL) was stirred under constant-potential electrolysis (-0.60 V vs Ag/Ag⁺) at 25 °C for 10 min under an N₂ atmosphere.

¹⁸O-Labeling Experiment using H₂¹⁸O. The formation of ¹⁸O₂ was confirmed by the GC-MS analysis of the gas generated at the anode after an 11 h reaction of MCH conducted under the following condition (Figure 1B). A mixture of MCH (64.1 mg, 0.50 mmol), **1a**·TfO (12.2 mg, 0.025 mmol), LiOTf (78.0 mg, 0.50 mmol), CH₃CN (4.9 mL), and H₂¹⁸O (0.10 mL, 5.5 mmol) was stirred under constant-potential electrolysis (-0.60 V vs Ag/Ag⁺) at 25 °C for 11 h with air bubbling at 1 atm using a peristaltic pump (1.2 mL/min). After 11 h of electrolysis, gas bubbles generated at the anode were collected using a Hamilton syringe and subsequently analyzed by GC-MS.

Electrochemical Reaction of MCH Using a Divided Cell. The electrochemical oxygenation was conducted utilizing ElectraSyn 2.0 (IKA) with a divided cell (IKA), with a 5 mL three-electrode setup, consisting of two Pt foil electrodes and an Ag/Ag⁺ reference electrode. In the cathode chamber, a mixture of MCH (64.0 mg, 0.50 mmol), LiOTf (78.0 mg, 0.50 mmol), **1a**·**TfO** (12.2 mg, 0.025 mmol), CH₃CN (4.0 mL), and H₂O (1.0 mL) was added. In the anode chamber, a mixture of LiOTf (78.0 mg, 0.50 mmol), CH₃CN (4.0 mL), and H₂O (1.0 mL) was added. The mixture was stirred under constant-potential electrolysis (-0.60 V vs Ag/Ag⁺) at 25 °C with air bubbling at 1 atm using a peristatic pump (1.2 mL/min). After 7.5 h of electrolysis, the crude product was esterified with trimethylsilyldiazomethane (TMSCHN₂) in the presence of methanol, and the resulting methyl ester of **AA** was analyzed by GC. The desired product was obtained in less than 1% yield. In addition, the yield remained similarly low (less than 1%) when **1a**·**TfO** (12.2 mg, 0.025 mmol) was added to each of the cathode and anode chambers.

ESI-MS analysis of 14b

The formation of the reaction intermediate **14b** was confirmed by the ESI-MS measurement of the reaction mixture obtained after 2 h reaction of **HCH** conducted under the following condition (Figure S1). A mixture of **HCH** (57.6 mg, 0.51 mmol), LiOTf (39.5 mg, 0.25 mmol), **1a**·**TfO** (12.2 mg, 0.025 mmol), CH₃CN (4.0 mL), and H₂O (1.0 mL) was stirred at 25 °C for 2 h with air bubbling at 1 atm using a peristatic pump.

Figure S1. ESI-TOF mass spectra of the reaction mixture of HCH.



4. Optimization of Reaction Conditions

In order to optimize the reaction condition for the electrochemical oxygenation of **MCH**, the effects of diverse electrodes, electrolytes, method of air introduction, cathode potential, and solvents were elucidated as shown in Table S1.

Table S1. Optimization of the reaction conditions.

		0				_					
	OMe			constant voltage 1a·TfO (5 mol%)			+ +	HO		<mark>О</mark> Н	
мсн			air (1 atm) electrolyte (0.1 solvent, 25 °	M) C	5			AA			
entry ^a	eleo anode	ctrode ^b cathode	electrolyte	introduction of air	cathode potential (V)	solvent	time (h)	conv. (%)	yield of 5 (%) ^c	yield of AA (%) ^c	total yield of 5 and AA (%) ^c
1	Pt	Pt	LiClO ₄	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	5	98	41	15	56
2	Pt	С	LiClO ₄	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	7	94	17	6	23
3	С	Pt	LiClO ₄	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	11	82	4	4	8
4	С	С	LiClO ₄	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	8	16	0	1	1
5	Ni	Pt	LiClO ₄	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	8	56	0	1	1
6	Pt	Pt	Bu ₄ NClO ₄	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	8	98	33	37	70
7	Pt	Pt	NaClO ₄	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	10	97	30	11	41
8	Pt	Pt	Bu_4NBF_4	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	12	96	49	33	82
9	Pt	Pt	Bu_4NPF_6	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	12	98	16	48	64
10	Pt	Pt	LiOTf	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	13	93	60	25	85
11	Pt	Pt	NaOTf	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	16	>99	26	27	53
12	Pt	Pt	KOTf	air balloon	-0.60	CH ₃ CN/H ₂ O (9:1)	15	91	39	20	59
13	Pt	Pt	LiOTf	open air	-0.60	CH ₃ CN/H ₂ O (9:1)	4	>99	32	29	61
14	Pt	Pt	LiOTf	bubbling (0.24 mL/min)	-0.60	CH ₃ CN/H ₂ O (9:1)	9	>99	33	47	80
15	Pt	Pt	LiOTf	bubbling (1.2 mL/min)	-0.60	CH ₃ CN/H ₂ O (9:1)	6	>99	13	68	81
16	Pt	Pt	LiOTf	bubbling (1.2 mL/min)	-0.30	CH ₃ CN/H ₂ O (9:1)	14.5	>99	10	57	67
17	Pt	Pt	LiOTf	bubbling (1.2 mL/min)	-0.90	CH ₃ CN/H ₂ O (9:1)	5.5	>99	13	67	80
18	Pt	Pt	LiOTf	bubbling (1.2 mL/min)	-0.60	CH ₃ CN/H ₂ O (4:1)	5.5	>99	12	78	90
19	Pt	Pt	LiOTf	bubbling (1.2 mL/min)	-0.60	CH ₃ CN/H ₂ O (49:1)	8.5	>99	12	69	81
20	Pt	Pt	LiOTf	bubbling (1.2 mL/min)	-0.60	CH ₃ CN	8.5	65	4	17	21
21	Pt	Pt	LiOTf	bubbling (1.2 mL/min)	-0.60	CH ₃ OH/H ₂ O (9:1)	13.5	97	38	13	51
22	Pt	Pt	LiOTf	bubbling (1.2 mL/min)	-0.60	TFE/H ₂ O (9:1)	11.5	>99	0	43	43

^a Conditions: **MCH** (0.5 mmol, 0.1 M), **1a·TfO** (5 mol%), electrolyte (0.1 M), and solvent under constant voltage electrolysis under air (1 atm) at 25 °C. The conversion and yield were determined by GC using biphenyl as an internal standard. ^b Electrode: Pt = platinum foil, C = carbon (graphite), Ni = nickel. ^c Detected as the corresponding methyl ester after esterification with TMSCHN₂.



Spectrum S2. ${}^{13}C{}^{1}H$ NMR ((CD₃)₂CO, 126 MHz) spectrum of AA.



Spectrum S3. ¹H NMR ((CD₃)₂SO, 500 MHz) spectrum of 7.



Spectrum S4. ${}^{13}C{}^{1}H$ NMR ((CD₃)₂SO, 126 MHz) spectrum of 7.

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